PAPER

Pupil findings in a consecutive series of 150 patients with generalised autonomic neuropathy

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Aim: To detect and characterise the pattern and extent of pupil abnormalities in patients with generalised autonomic failure.

Methods: A consecutive series of 150 patients referred for investigation of symptomatic generalised autonomic failure underwent pupil investigations. Infra-red video pupillography was used to measure resting pupil diameters in light and dark, the light reflex response, the miosis associated with an accommodative effort, and responses to topical administration of various pharmacological agents. The results were compared with data recorded under identical conditions from a cohort of 315 age-matched and sex-matched healthy controls.

Results: Overall, two thirds of patients had abnormal pupils (66%) with sympathetic deficit occurring twice as often as parasympathetic deficit. However, the prevalence and type of pupil abnormality showed wide variation according to aetiology—for example, almost all patients with amyloidosis had abnormal pupils, two thirds with pure autonomic failure but less than a quarter with multiple system atrophy. In most patients (85%), pupil abnormalities were bilateral and symmetrical, none had a Horner's syndrome in one eye and a tonic pupil in the other. No significant correlation between the type of pupil abnormality and the predominant type of systemic autonomic deficit was seen in most conditions.

Conclusions: The pupils are often affected in autonomic neuropathy, although this is not always apparent either to the patient or to their doctors. Considerable care is needed not only to detect these abnormalities but also to interpret correctly the results of pupil tests in this group of patients.

Both sympathetic and parasympathetic branches of the autonomic nervous system innervate the iris muscles, and so it is reasonable to expect that conditions characterised by generalised autonomic neuropathy will affect the pupil. Parasympathetic dysfunction might cause relative mydriasis of the pupil in the light, attenuation of the light response and pupillotonia (if there is aberrant reinnervation).[1] Sympathetic dysfunction might cause relative miosis of the pupil in the dark, redilatation lag,[2] and attenuation of the startle reflex. In either case the denervated pupil is expected to develop supersensitivity to dilute agonists (eg, 1% phenylephrine for the dilator muscle, 0.1% pilocarpine for the sphincter muscle).

bnormal pupils indicating damage to either parasympathetic or sympathetic nerves have often been reported in association with generalised autonomic neuropathy.[3] However, most of these reports are anecdotal and based only on a clinical examination (where the pick-up rate is expected to be low for bilateral symmetrical deficits) or pharmacological tests (where dry eyes causing increased trans-corneal drug penetration into the eye may give rise to false-positive results). No systematic studies have been conducted to assess the prevalence of pupil abnormalities, nor is it known how the pupil signs correlate with the underlying diagnosis or the pattern of autonomic deficits seen elsewhere in the body.

In this study we carefully examined the pupils of an unselected consecutive series of 150 patients, all of whom have generalised autonomic neuropathy. We characterised the pupil abnormalities, estimated their prevalence in different conditions and attempted to draw correlations between the pupil signs and the overall neurological picture. A preliminary account of some of these data has already been presented.[4]

METHODS

Patients

In total, 150 patients (87M/63F) aged 15–80 years, consecutive referrals for pupil or autonomic function tests, were recruited to this study (table 1). All had symptomatic autonomic neuropathy with abnormal objective autonomic function tests. Diagnoses, made by the referring doctors from standard criteria, included amyloidosis (n = 21; 15 acquired (all but one of which were typed as light-chain amyloidosis) and 6 familial), multiple system atrophy (MSA) (n = 38), pure autonomic failure (PAF) (n = 33), diabetes mellitus (n = 29) and a miscellaneous group (n = 29) comprising hereditary sensory and autonomic neuropathy (HSAN) type I (n = 1), HSAN type II (n = 2), HSAN type III or Riley-Day syndrome (n = 2), hereditary motor and sensory neuropathy (HMSN) type II (n = 1), paraneoplastic syndromes (n = 6), acute dysautonomia (n = 1), subacute dysautonomia (n = 3), post-encephalitic dysautonomia (n = 1), triple A (Allgrove's) syndrome (n = 2 sibling pairs), Sjögren's syndrome (n = 3), paraproteinaemia without evidence of amyloidosis (n = 1), inherited sympathetic neuropathy (n = 2 siblings) and dopamine-β-hydroxylase deficiency (n = 2 siblings).

At the time of examination, no patient was receiving drug treatment, systemic or topical, likely to interfere with pupil function. Sympathomimetic drugs, prescribed for postural hypotension in some patients with MSA, PAF or dopamine-β-hydroxylase deficiency, were stopped overnight. All patients and controls participating in this study gave their informed consent for these investigations according to the

Abbreviations: HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; MSA, multiple system atrophy; PAF, pure autonomic failure

Table 1 Patient and control characteristics

Diagnosis	N	M	F	Median age	Age range Min	Age range Max
Amyloidosis	21	14	7	57	31	70
MSA	38	26	12	58	40	79
PAF	33	15	18	60	30	80
Diabetes	29	16	13	46	19	76
Miscellaneous	29	16	13	39	15	75
All patients	150	87	63	54	15	80
Controls	315	172	143	42	17	82

F, female; M, male; Max, maximum; Min, minimum; MSA, multiple system atrophy; N, number; PAF, pure autonomic failure.

Declaration of Helsinki, and the local ethics committee approved the study.

Pupillography

Pupil diameters and their responses to light and to an accommodative effort (near) were recorded with an infrared television pupillometer (Whittaker/Applied Science Laboratories, Bedford, MA, USA) as previously described.[5] Pupil diameters were recorded in darkness and in light, and near responses (to a target at 18 cm distance) under dim ambient illumination. Light reflexes were induced with xenon arc or light-emitting diode white illumination, for 1 s duration at 10-s intervals, at an intensity sufficient to produce the largest possible reflex for each patient. Pupillotonia was sought by inspection of the rate of constriction in response to continuous bright illumination. Iris sympathetic function was assessed by measuring the $T_{¼}$ redilatation time during recovery from the light reflex[6] as originally described by Pilley and Thompson.[7] Redilatation time was not recorded if the pupils were tonic. Eyes with past or present uveitis were excluded, as were any eyes that had had surgery or laser treatment or had visible rubeosis iridis.

Bilateral recordings were made wherever possible-and darkness anisocoria measured (expressed as right–left (R–L) diameters). For clarity and statistical analysis, the remaining measurements are presented for one eye only (R if available) per patient. Reduced pupil diameters in darkness and the redilatation lag were taken as indicators of sympathetic dysfunction, and reduced light reflexes or mydriasis in the light and pupillotonia as indicators of parasympathetic dysfunction. It was not always possible to obtain all measurements for every eye, usually because the particular patients were too disabled to undergo full examination. Thus in some patients only the dark diameter measurements are presented, and near reflexes were recorded in a limited number of patients from all groups (table 2).

Cholinergic and noradrenergic supersensitivity was sought in a few instances by application of single eyedrops of pilocarpine 0.1% and phenylephrine 1%, respectively, and sympathetic integrity with single eyedrops of cocaine 4%.

Statistical analysis

All measurements were compared with those obtained under identical conditions in 315 controls (172M/143F) aged 17–82 years. Some of these have been published previously but the numbers have now been increased and they are presented here (table 2, fig 1). Abnormality of each variable was defined as a value lying outside the normal 95% confidence intervals. Residual values for diameter versus age and redilatation time ($T_{¼}$) versus reflex amplitude were normally distributed. Because light reflex amplitude covaries with resting diameter,[8] the size of the pupil response to light was expressed as the ratio reflex amplitude/starting diameter, values of which were normally distributed in controls. Near responses were assessed similarly. Categorical differences between patient groups were assessed using the χ^2 test. Differences in pupil variables were assessed non-parametrically using the Mann–Whitney U test.

The patients were subjected to multiple pupil function tests, seven of which define abnormality quantitatively as a value lying >2 standard deviations outside the mean (one tailed in all patients). In this scenario of multiple testing, for any given patient, the probability-p, of observing a single abnormal result by chance alone is 0.15; such a result has been dismissed as insignificant. We accepted pupil abnormalities as significant only if two or more tests lay outside the normal range ($p<0.012$) or a single abnormal result lay outside one 99.5% confidence interval ($p = 0.034$). As tonic pupils or Horner's syndrome do not occur in controls, these abnormalities were always accepted as significant.

RESULTS

All patients

Pupil abnormalities in the 150 patients are summarised in table 3 and the significance of differences between the four main groups of patients in table 4. Overall, pupil abnormality was found in 99 of 150 (66%) patients. This contrasts with the results from controls. Of the 315 controls examined, 50 were submitted to all seven tests and of these 9 (18%) had at least one abnormality significant at the 5% level ($p<0.05$). In the context of multiple testing, this does not differ significantly from the expected value of 14.1% ($\chi^2 = 0.282$; $p = 0.595$). Applying the same criteria used to define abnormality in the patient group (see Methods), 3 of the 50 controls (6%) had either two abnormalities at the 5% level or one abnormality at the 1% level; this does not differ significantly from the expected value of 4.6% ($\chi^2 = 0.98$; $p = 0.755$).

There was some variation in the frequency with which different types of pupil abnormality were observed in the patient group: considerable miosis in the dark was observed in 25.3% (fig 1A), mydriasis in the light in 18.9%, anisocoria in 16.4%, a reduced-light reflex in 22.6%, a reduced near reflex in 12.1% and light–near dissociation in 13.2% of patients. Bilateral pupillotonia was observed in 25 (17.1%) patients; among these, 13 had miosis in the dark, 21 had reduced light reflexes and 12 showed light–near dissociation. Unilateral pupillotonia was not seen in any patient. Bilateral Horner's syndrome was found in 43/112 (38.4%) patients (fig 1B); 10 of them had miosis in the dark. The frequencies of these results of individual tests differ from the expected frequencies at $p \leqslant 0.01$. Pupil characteristics of eyes with bilateral pupillotonia and bilateral Horner's syndrome are compared in table 5.

Amyloidosis

All but one of the 21 patients studied had abnormal pupils. Six had bilateral pupillotonia with reduced-light reflexes; two of these showed light–near dissociation, three had miosis in the dark and two had notable anisocoria (>0.7 mm). Ten patients had bilateral Horner's syndrome with normal light reflex amplitudes but redilatation lag (fig 1B); one of these had miosis in the dark, one had anisocoria. Two patients had unilateral Horner's syndrome and two others had darkness miosis. The overall prevalence of pupil abnormality in this group (95.2%) does not differ significantly from 100% (95% confidence intervals (CI) 76% to 100%).

Multiple system atrophy

None of the 38 patients had bilateral pupillotonia or bilateral Horner's syndrome. Eight patients had unilateral Horner's syndrome; two of them with marked anisocoria, one with

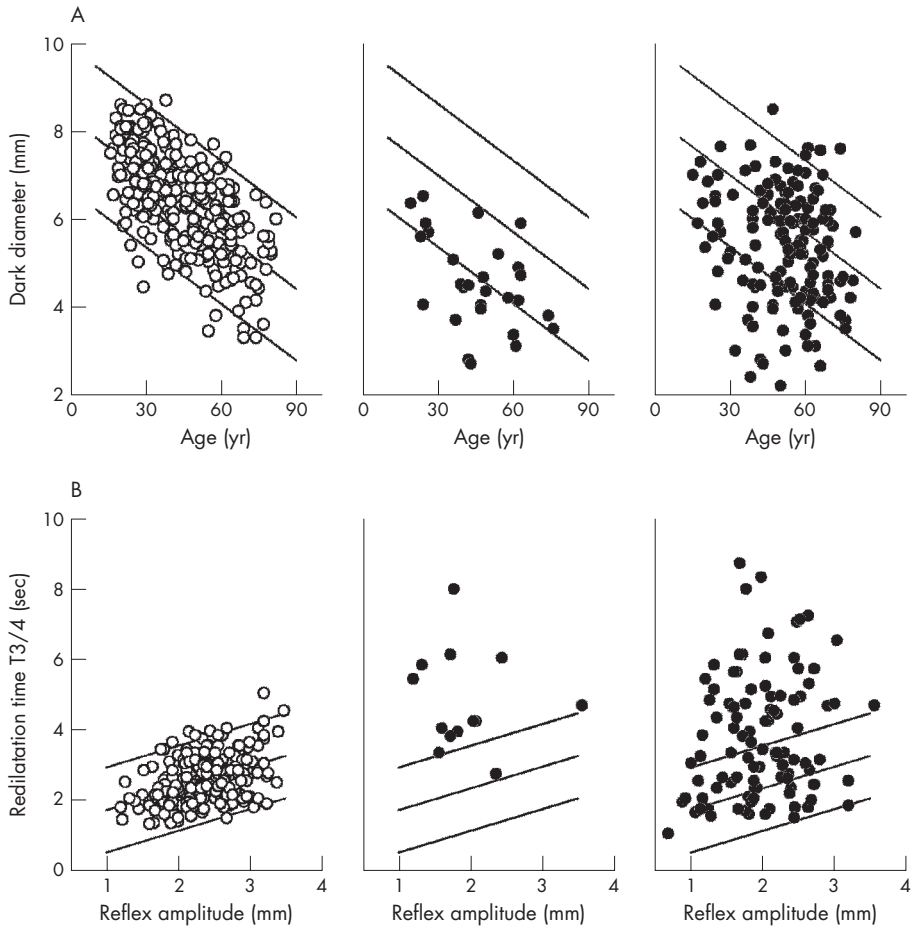

Figure 1 (A) Relationship between age and pupil dark diameter in healthy controls (left), patients with diabetes (middle) and all patients with autonomic failure included in this study (right). (B) Relationship between reflex amplitude and redilatation time in healthy controls (left), patients with amyloid (middle) and all patients with autonomic failure included in this study (right).

diminished light reflexes. One of these patients had a history of harlequin syndrome on the affected side. One other patient had diminished light reflexes, but was at the time taking anti-cholinergic anti-Parkinson medication, which could have been responsible. Twenty six patients had normal pupils. The overall prevalence of pupil abnormality was 31.6% (95% CI 17% to 49%).

Pure autonomic failure

Sixteen of the 33 patients had bilateral Horner's syndrome (two with miosis and two with considerable anisocoria). One of these patients had a history of harlequin syndrome (one side). Unilateral Horner's syndrome was found in one of the 33 patients. Two patients had bilateral pupillotonia. Three other patients had reduced light and near reflexes, two of them with miosis. The overall prevalence of pupil abnormality was 66.7% (95% CI 48% to 82%).

Diabetes

Six of the 29 patients had bilateral pupillotonia and reduced light reflexes (five of these with miosis and three with light–near dissociation). Nine patients had bilateral and two had unilateral Horner's syndrome (five of them with miosis). Of the 12 remaining patients, four had miosis and four had reduced light reflexes or mydriasis in the light. Fourteen of the 29 patients had abnormally small pupils (fig 1A). Normal pupils were observed in seven patients. The overall prevalence of pupil abnormality was 75.9% (95% CI 56% to 90%).

Table 2 Normal values

Variable	n	Expected value	Confidence intervals	
			95%	99%
Dark diameter (mm)	315	8.283–(0.043*A)	±1.63†	±2.16†
Light diameter (mm)	132	−0.199 + (0.536*D)	±1.01†	±1.33†
Dark anisocoria (mm)	168	0.28	<0.70	<1.05
Light reflex ratio	246	0.368	±0.138	±0.180
$T_{¼}$ redilatation time (s)	225	1.048 + (0.619*R)	±1.21†	±1.59†
Near reflex ratio	117	0.246	±0.169	±0.223
Light–near reflex ratio	91	0.130	±0.198	±0.262

A, age (years); D, dark diameter (mm); R, reflex amplitude (mm).
†Averaged over the whole range. *Multiplied by.

Table 3 Summary of pupil abnormalities in autonomic neuropathy

Patient group	n	Bilateral tonic pupils	Bilateral Horner's syndrome	Unilateral Horner's syndrome	Other	Total abnormal	Total normal*
Amyloidosis	21	6	10	2	2	20	1 (0)
MSA	38	0	0	8	4	12	26 (5)
PAF	33	2	16	1	3	22	11 (1)
Diabetes	29	6	9	2	5	22	7 (4)
Miscellaneous	29	11	8	2	2	23	6 (1)
All	150	25	43	15	16	99	51 (11)

MSA, multiple system atrophy; PAF, pure autonomic failure.
*Figures in parentheses indicate the number of these patients with one pupil abnormality significant at $p<0.05$; in the context of multiple testing we have classified these cases as normal (see Methods). The remaining patients classified as normal had no significant pupil abnormalities.

Differences between conditions

The prevalence of each pupil abnormality in these four conditions is given in table 4 and the significance of any differences is indicated. Bilateral miosis in the dark, pupillotonia, a reduction in the response to light and light–near dissociation are common features of diabetic autonomic neuropathy, occur somewhat less frequently in amyloidosis, but are found rarely in PAF and not found in MSA. By contrast, bilateral Horner's syndrome occurs commonly in amyloidosis, PAF and diabetes, but not in MSA. The diagnostic test for distinction between PAF and MSA yielded 54.5% sensitivity and 100% specificity for the occurrence of bilateral Horner's syndrome or bilateral pupillotonia in PAF.

Miscellaneous group of patients

Four of six patients with inherited neuropathies had abnormal pupils. One patient with HMSN II (CMT 2) had bilateral tonic pupils with reduced-light reflexes and light–near dissociation. One patient with HSAN I had normal pupils despite severe generalised autonomic failure. One patient with HSAN II had

Table 4 Differences between diagnostic groups

Numbers of abnormalities and group percentages							
Variable	**Groups**					**χ^2**	**p Value**
Miosis in dark	Normal	MSA	PAF	Amyloid	Diabetes		
n	11/315	2/38	4/33	6/21	14/29	81.21	<0.001
%	3.5	5.3	12.1	28.6	48.3		
Mydriasis in light	Normal	MSA	PAF	Amyloid	Diabetes		
n	8/176	1/29	1/26	3/16	8/18	39.61	<0.001
%	4.5	3.4	3.8	18.8	44.4		
Dark anisocoria	Normal	PAF	Diabetes	MSA	Amyloid		
n	5/168	2/32	2/24	5/35	3/20	9.94	0.041
%	3.0	6.3	8.3	14.3	15.0		
Reduced light reflex	Normal	MSA	PAF	Diabetes	Amyloid		
n	5/246	3/38	3/31	8/28	7/21	51.12	<0.001
%	2.0	7.9	9.7	28.6	33.3		
Reduced near reflex	Normal	MSA	Amyloid	Diabetes	PAF		
n	2/117	2/26	1/12	1/7	5/24	14.47	0.006
%	1.7	7.7	8.3	14.3	20.8		
Bilateral tonic pupils	Normal	MSA	PAF	Diabetes	Amyloid		
n	0/241	0/37	2/33	6/29	6/19	72.35	<0.001
%	0.0	0.0	6.1	20.7	31.6		
Unilateral tonic pupils	Normal	PAF	MSA	Diabetes	Amyloid		
n	0/241	0/37	0/33	0/29	0/19	–	
%	0.0	0.0	0.0	0.0	0.0		
Bilateral Horner's syndrome	Normal	MSA	Diabetes	PAF	Amyloid		
n	0/241	0/37	9/19	16/28	10/13	188.24	<0.001
%	0.0	0.0	47.4	57.1	76.9		
Unilateral Horner's syndrome	Normal	PAF	Diabetes	Amyloid	MSA		
n	8/225	1/28	2/19	2/13	8/37	17.92	0.001
%	4.0	3.6	10.5	15.4	21.6		
Light–near dissociation	Normal	MSA	PAF	Amyloid	Diabetes		
n	2/91	0/26	0/24	2/12	3/7	32.43	<0.001
%	2.2	0.0	0.0	16.7	42.9		
Any abnormality	Normal	MSA	PAF	Diabetes	Amyloid		
n	12/315	14/38	22/33	22/29	20/21	228.56	<0.001
%	4.6	36.8	66.7	75.9	95.2		

MSA, multiple system atrophy; PAF, pure autonomic failure.
The normal group is placed in the lefthand column. The patient groups are arranged in order of percentage abnormality. Common underlining indicates overlapping 95% exact confidence intervals—that is, no significant difference between the groups.

Table 5 Pupil characteristics in patients with bilateral tonic pupils or bilateral Horner's syndrome

	Bilateral tonic pupils		Bilateral Horner's syndrome			
Median age	46		52			
Male/Female	13/12		26/17			
Variable	n	%	n	%	χ^2	p Value
Miosis in dark	13/25	52.0	10/43	23.3	5.835	0.016
Anisocoria	6/25	24.0	6/42	14.3	1.006	0.316
Mydriasis in light	15/20	75.0	0/33	0.0	34.520	<0.001
Reduced-light reflex	21/25	84.0	0/43	0.0	52.259	<0.001
Reduced-near reflex	1/23	4.3	4/27	14.8	1.512	0.219
Light–near dissociation	12/23	52.2	0/27	0.0	18.535	<0.001

bilateral tonic pupils with impaired constriction to light and light–near dissociation. Another patient had normal pupils. Both patients with HSAN III (familial dysautonomia) had abnormal pupils; in each case the pupils were miotic, and in one patient there was bilateral Horner's syndrome.

Four of six patients with dysautonomia associated with paraneoplastic states had abnormal pupils. Two of them had bilateral tonic pupils with reduced light reflexes, and in one of them there was light–near dissociation. One patient whose dysautonomia was predominantly sympathetic had bilateral Horner's syndrome, and in one patient with Lambert–Eaton syndrome there was unilateral Horner's syndrome and also supersensitivity to pilocarpine and phenylephrine.

All four patients with acute or subacute dysautonomia had abnormal pupils. In one case the pupils were of medium size but unreactive to both light and near; the pupils were supersensitive to both phenylephrine and pilocarpine, and 0.1% pilocarpine also induced three dioptres of myopia indicating ciliary muscle denervation. One patient had bilateral tonic pupils with light–near dissociation. There was one patient with bilateral and one with unilateral Horner's syndrome.

Three of four patients with Triple A syndrome had bilateral tonic pupils, but without light–near dissociation. The fourth had normal pupils.

All four patients with an inherited pure sympathetic neuropathy (two with dopamine hydroxylase deficiency and two of unknown aetiology) had bilateral Horner's syndrome with light and near reflexes of normal amplitude, but with redilatation lag and supersensitivity to phenylephrine. In the two siblings with dopamine hydroxylase deficiency, stopping their dihydroxyphenylserine treatment did not affect the pupil findings.

Two of three patients with Sjögren's syndrome had bilateral tonic pupils with reduced-light reflexes and light–near dissociation. The third patient had normal pupils. The only patient with isolated paraproteinaemia and post-encephalitic dysautonomia had bilateral tonic pupils with absent light reflexes and light–near dissociation.

Six patients in this miscellaneous group had normal pupils. The overall prevalence of pupil abnormality was 79.3% (95% CI 60% to 92%).

Drug tests

Pharmacological tests using topically applied eye drops were carried out on 26 of the 150 patients. All of seven patients tested were supersensitive to pilocarpine; these included four patients who had bilateral Horner's syndrome. Ten of 13 tested showed diminished responses to 4% cocaine; these included three patients who had bilateral tonic pupils. Thirteen of 19 patients tested were supersensitive to phenylephrine; these included seven of nine patients with bilateral Horner's syndrome and six of seven patients with miosed hyporeflexic pupils due to diabetes.

Correlation of pupil findings with pattern of systemic autonomic deficits

The observed frequencies of systemic and pupillary deficits in 140 patients are shown in table 6 (information about the systemic autonomic profile in the remaining patients was not available). Although there does appear to be some weak correspondence between our pupillographic findings and the results of autonomic function tests, a χ^2 test suggests that this association could have arisen by chance ($p = 0.072$).

DISCUSSION

This study is the first systematic investigation of pupil findings in an unselected cohort of patients with generalised autonomic failure. The overall prevalence of pupil abnormality was around 66% or two thirds of the patients. This means that one in three patients with widespread autonomic failure appears to have normal pupils; it is not clear whether such ''pupil-sparing'' reflects limited sensitivity in the tests used to detect pupil abnormalities or whether it indicates that damage to autonomic nerves is patchy (as is known to be the case elsewhere in the body) and does not always affect the pupil.

The prevalence of pupil abnormality varied considerably according to aetiology. Abnormal pupils were almost always seen in some conditions (eg, diabetes, amyloidosis, acute or subacute dysautonomia), were often found in others (PAF, paraneoplastic states) but were not common in MSA, where the damage is thought to be in the central nervous system rather than the peripheral nerves. If patients with MSA are set aside, then the overall prevalence of pupil abnormality in all other types of generalised dysautonomia was 78%. In some conditions the prevalence of pupil abnormality in our study was much greater than that reported in the literature (amyloidosis, PAF, HSAN type III), perhaps reflecting greater sensitivity for detecting pupil abnormalities using our techniques.

As expected, in most patients with abnormal pupils the deficits were bilateral and symmetrical (85%). Sympathetic deficits were twice as common overall compared with parasympathetic deficits, but the balance of autonomic failure varied with aetiology. In some conditions the observed pupil abnormalities always indicated sympathetic loss (dopamine β-hydroxylase deficiency, MSA, HSAN type III) and in others parasympathetic loss (Triple A syndrome, Sjögren's syndrome), but in most conditions a mixture of sympathetic and parasympathetic deficits were observed (amyloidosis, PAF, diabetes, paraneoplastic states, acute and subacute dysautonomia). Among patients with bilateral tonic pupils only half showed light–near dissociation, mainly because both near and light responses were attenuated (although this

Table 6 Relationship between pupil and generalised autonomic deficits

	Generalised autonomic features			
	Sympathetic deficits	**Parasympathetic deficits**	**Both deficits**	**Sum**
Patients with normal pupils	3	5	42	50
Patients with pupils showing sympathetic deficit alone	13	2	36	51
Patients with pupils showing parasympathetic deficit alone	3	4	12	19
Patients with pupils showing both deficits	1	2	17	20
All patients	20	13	107	140

For patients with pupil abnormality: $\chi^2 = 8.609$ for 4 df, $p = 0.072$.

reduction in near response amplitude was significant in only 1/23 cases). This contrasts with pupil findings in patients with Holmes–Adie syndrome, in which patients usually have light–near dissociation associated with exaggerated near responses. We suggest that the chronic progressive damage to the parasympathetic fibres that occurs in generalised dysautonomias allows little opportunity for the (aberrant) regeneration that occurs in Holmes–Adie syndrome.

We had expected the pattern of pupil abnormality to reflect the pattern of autonomic failure in other systems in each patient: patients with predominant loss of sympathetic function might have bilateral Horner's syndrome whereas patients with predominant parasympathetic failure might have bilateral pupillotonia. In this series most patients showed a mixed pattern of generalised autonomic failure, and the predominant deficit did not predict the pattern of pupil abnormality.

Most of the abnormal pupils identified in this study were not suspected either by either the patients or by the referring clinicians. This is in part owing to the preponderance of bilateral symmetrical deficits, which are difficult to detect clinically, especially if the defect is sympathetic. In almost all cases the patients had no associated ocular or visual symptoms even if the pupils were tonic with associated accommodative paresis. Some of the patients also underwent a complete ophthalmic examination but the only other ocular abnormalities found were dry eyes due to aqueous insufficiency in the tear film. It seems that autonomic denervation of the eye in the context of widespread autonomic failure generates few symptoms or signs and rarely needs treatment other than the regular use of artificial tear drops.

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